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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,847	12/12/2000	C. Frank Bennett	ISPH-0524	4732

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EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/734,847	Applicant(s) BENNETT ET AL.	
	Examiner Janet L Epps-Ford, Ph.D.	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. The election/restriction requirement set forth in the prior Office Action is hereby withdrawn by the Examiner.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-3, 6-13, 21-26, and 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Kole et al. (WO94/26887-A1).

Kole et al. teach a method of altering the splicing of a pre-mRNA. This method comprises hybridizing an antisense oligonucleotide to the pre-mRNA molecule to create a duplex molecule under conditions that permit splicing. The antisense oligonucleotide is one that does not activate RNAse H, and is selected to block a member of the aberrant set of splice elements so that the native intron is removed by the use of normal splice elements so that the mRNA encoding the native protein is produced (page 6 through page 8, line 17). The antisense oligonucleotides used in this method contain at least one, or all of the internucleotide bridging phosphate residues are modified phosphates selected from the group consisting of: methyl phosphonates, methyl phosphonothioates, phosphoromorpholidates, phosphoropiperazidates, and phosphoramidates, and may contain a nucleotide having a lower alkyl substituent at the 2'

position thereof (page 9, lines 4-26). In regards to the modulation of splicing that results in an altered ratio of splice products, and exclusion of one or more exons from the mature mRNA see

The antisense oligonucleotides of Kole et al. may be designed to block a mutated element, a cryptic element, or a native element such as a 5' splice site, a 3' splice site (which correspond to an intron-exon borders), or a branch point (page 8, lines 5-10). The methods of Kole et al. are disclosed as being useful for targeting human pre-mRNA encoding beta-, and alpha-globin, beat-hexoseaminidase, phenylalanine hydroxylase, and cystic fibrosis gene premRNA (which is known in the art to encode a membrane protein; see bridging paragraph pages 10-11).

Kole et al. teach each and every aspect of the instant invention thereby anticipating applicant's claimed invention.

4. Claims 1-2, 5-13, and 16-19 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hodges et al. (Mol. Pharmacol. (1995), 48(5), 905-18.)

Hodges et al. report the construction, characterization, and use of luciferase reporters to test the ability of antisense oligonucleotides to inhibit RNA splicing. β-Globin and adenovirus introns were inserted into a luciferase cDNA, and luciferase expression was analyzed in transiently transfected cells. Wild-type and 3'- splice site-mutated adenovirus reporters were used to determine the ability of phosphorothioate deoxy and 2'-methoxy oligonucleotides to inhibit splicing. Rnase-H activating oligodeoxynucleotides were better inhibitors of wild-type adenovirus expression than were 2'-methoxy analogs (see 905 and 907). However, 2'-methoxy oligonucleotides specific for the branchpoint were more effective inhibitors of splicing of adenovirus transcript containing the β-globin branchpoint and 3'- splice site. Furthermore,

Hodges et al. teach that pre-mRNAs with weak splice sites are potential targets for oligonucleotides that inhibit splicing by occupancy rather than cleavage of the transcripts. In addition, Hodges et al. teach that the observation that in some cases oligonucleotides that do not serve as substrates for RNase H may enhance production of a target protein may be quite important, since it suggests the possibility that antisense oligonucleotides may be designed to increase rather than inhibit production of a therapeutically important target (p. 917).

Hodges et al. teach each and every aspect of the instant invention thereby anticipating applicant's claimed invention.

5. Claims 1, 6, 14-17, and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al. (WO 9304701 A1)

Wu et al. teach the use of oligonucleotide-binding agents to target the polyadenylation signal of hepatitis B viral mRNA. This oligonucleotide-binding agent forms a complex with its target mRNA. In one embodiment, Wu et al. teach use of an oligonucleotide-binding agent that is capable of blocking translation of the hepatitis B viral mRNA. Wu et al. also teach that this method can be used to block production of hepatitis virus if the antisense oligonucleotide is delivered directly to liver cells, this is accomplished by the use of a polylysine binding agent (page 10, lines 1-17). Page 4, of Wu et al. teach that the preferred antisense oligonucleotides can be analogues comprising, for example, wherein one of the phosphate oxygen is replaced by a sulfur atom (see lines 19-24).

Wu et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

6. Claims 1-2, 5-19, and 29-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Moulds et al.

Moulds et al. teach the design of antisense oligonucleotides having such high affinity for RNA that they form a nearly irreversible complex, thereby inactivating the RNA via a non-RNAse H, or steric block mechanism (p. 5045, para. 2). Moulds et al. disclose modified antisense oligonucleotides comprising phosphorothioate, 2'-O-allly, and C-5 propyne modifications. Moulds et al. teach a splicing assay using C-5 propyne, phosphorothioate modified oligonucleotides targeting the 5'-splice site of TAg RNA. The presence of this oligonucleotide complexed to Tag RNA resulted in 100% inhibition of splicing and blocked translation of the RNA (see table 4, page 5051). The oligonucleotides of Moulds et al. are designed to target 5'-splice junctions, and polyadenylation signals, see for example Table 1.

Mould et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-31 of U.S. Patent No. 6,210,892.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

9. Claims 1-33 of the issued US patent are obvious over claims 1-33 of the instant application. The claims of the instant application differ from the issued claims to the extent that the instant claims are broader than the instant claims. Additionally, the claims of the issued US Patent differ from claims 26-28 to the extent that they do not recite peptide nucleic acid having a lysine residue at its C-terminus or peptide nucleic acid having an arginine residue at its C-terminus. For example, claim 1 of the instant application is drawn broadly to a method of controlling the behavior of a cell through modulation of the processing of a selected wild-type mRNa target within said cell, comprising binding to said target and antisense compound that does not elicit cleavage of the mRNA target. The claims of the issued US Patent encompass the same method however the issued claims are limited to the use of specifically modified antisense oligonucleotides that do not elicit cleavage of an mRNA target. The issued claims are limited to those antisense oligonucleotides comprising at least one 2'-methoxyethoxy, 2'-dimethylaminooxyethoxy, 2'-dimethylaminoethoxyethoxy, 2'-acetamide, morpholino, or peptide nucleic acid modification. At the time of filing of the instant application it would have been

obvious to one of ordinary skill in the art at the time of filing to modify, for example, claim 1 of the instant application to recite these modifications since they are clearly disclosed in the specification as filed as modifications which do not elicit cleavage of an mRNA target. Moreover, one having ordinary skill in the art would have been motivated to do this because these embodiments are disclosed as being a preferred embodiment within claims 3-4, and 20.

Additionally, in regards to instant claims 26-28, which recite peptide nucleic acid having a lysine residue at its C-terminus or peptide nucleic acid having an arginine residue at its C-terminus, these claims are an obvious variation of claims 1-31 of the issued US Patent since oligonucleotides modified with a polylysine group since this modification is disclosed in the specification of the US Patent (col. 23, lines 37-44) as enhancing cellular uptake of oligonucleotides at the cellular level. Moreover, one having ordinary skill in the art would have been motivated to do this because these embodiments are disclosed as being a preferred embodiment in the issued US Patent.

Therefore, the invention as a whole is *prima facie* obvious over Bennett et al. (US Patent 6,210,892).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
February 28, 2003

SEAN McGARRY
PRIMARY EXAMINER